Patients with autosomal dominant polycystic kidney disease have elevated fibroblast growth factor 23 levels and a renal leak of phosphate

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Abstract: Fibroblast growth factor 23 (FGF23) and parathyroid hormone blood levels rise following progressive loss of renal function. Here we measured parameters of phosphate metabolism in 100 patients with autosomal dominant polycystic kidney disease (ADPKD) in stage 1 or 2 of chronic kidney disease, 20 patients with non-diabetic chronic kidney disease, and 26 with type 2 diabetes. Twenty healthy volunteers served as controls. The mean levels of FGF23 were significantly (4-fold) higher in ADPKD compared to non-diabetic and diabetic patients, and healthy volunteers. Mean serum phosphate levels were significantly lower in ADPKD patients compared to non-diabetic and diabetic patients, and the healthy volunteers. The prevalence of hypophosphatemia was 38, 25, 27, and 5% in ADPKD, non-diabetic and diabetic patients, and healthy volunteers, respectively. The tubular maximum of phosphate reabsorption per glomerular filtration rate was lowest in ADPKD patients with a significantly high positive correlation with serum phosphate levels. Estimated glomerular filtration rates were approximately 100 ml/min per 1.73 m(2) in all groups and parathyroid hormone and vitamin D metabolite levels were in the normal range. Thus, FGF23 was substantially elevated in ADPKD patients compared to other CKD patients matched for glomerular filtration rate, and was associated with increased renal phosphate excretion. The mechanism for this anomaly will require further study.

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Elevated FGF23 levels in ADPKD patients with apparent renal leak of phosphate: A new manifestation of ADPKD.

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Abstract

Fibroblast growth factor 23 (FGF23) and parathyroid hormone blood levels rise following progressive loss of renal function. We analyzed FGF23 and other parameters of phosphate metabolism in chronic kidney disease stage 1 and 2 patients with autosomal dominant polycystic kidney disease (ADPKD) (n=100), non diabetic chronic kidney disease (n=20) and diabetes mellitus type 2 (n=26). Twenty healthy volunteers served as controls. Mean (SD) FGF23 levels were 4-fold higher in ADPKD (163±33 RU/ml) compared to non diabetic (44±18 RU/ml) patients, diabetic (40±56 RU/ml) patients and healthy volunteers (28±22 RU/ml) ($P<0.0001$). Mean serum phosphate levels were lowest in ADPKD patients (0.92±0.17 mmol/l ADPKD, 1.04±0.22 mmol/l non diabetic patients, 0.96±0.17 mmol/l diabetic patients, and 1.01±0.12 mmol/l healthy volunteers; $P=0.007$). The prevalence of hypophosphatemia was 38%, 25%, 27% and 5% ($P=0.03$) in ADPKD, non diabetic and diabetic patients, and healthy volunteers, respectively. The tubular maximum of phosphate reabsorption per glomerular filtration rate was lowest in ADPKD patients with a high positive correlation with serum phosphate levels ($r^2=0.86$, $P<0.0001$). Estimated glomerular filtration rate was approximately 100 ml/min/1.73 m^2 in all groups and parathyroid hormone and vitamin D metabolite levels were in the normal range. Elevated FGF23 levels and an apparent renal leak of phosphate represent a specific and newly recognized manifestation of early stage ADPKD.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a slowly progressive disease which is caused by mutations in *PKD1* or *PKD2*, the genes encoding for polycystin-1 and polycystin-2. The growing cysts gradually replace the functional renal parenchyma and distort the normal architecture of the kidney. Typically the volume of the kidney increases from normal (150-200 cm^3) in adolescence to 1000 cm^3 in young adults.[1-2] At an age between 20 and 40 years approximately 50% of the normal parenchyma is replaced by cysts. However, despite the presence of innumerable cysts in both kidneys, glomerular filtration rate (GFR) remains preserved up to age 40 in most patients, because glomerular hyperfiltration of functioning nephrons compensates for the ongoing loss of functional renal tissue.[3-4]

Fibroblast growth factor 23 (FGF23) is primarily secreted by osteocytes and regulates bone mineralization.[5] In the kidney, FGF23 binds to the canonical FGF receptor in the presence of the cofactor Klotho and suppresses renal tubular phosphate reabsorption and 1α-hydroxylase activity.[6] Hyperphosphaturia, decreased bone mass and osteomalacia are hallmarks of disorders with excessive FGF23 production and normal renal function which include autosomal dominant and recessive hypophosphatemic rickets[7], X-linked hypophosphatemia (XLH)[8] and oncogenic osteomalacia.[9] Markedly elevated circulating FGF23 levels are also found in patients with advanced chronic kidney disease (CKD). In such patients, the elevation of serum FGF23 levels is thought to counteract the retention of phosphate and is classically accompanied by a rise in parathyroid hormone (PTH) and a fall in 1,25-dihydroxyvitamin D levels.[10] However, whether the rise in serum FGF23 in patients with CKD precedes or follows the reduction in GFR remains a matter of debate.

The objective of the present investigation was to measure FGF23 serum levels in a cohort of ADPKD patients with CKD stage 1 and 2 and to correlate serum FGF23 levels with parameters of phosphate metabolism, including renal phosphate excretion, serum PTH levels and levels of vitamin D metabolites. Surprisingly, FGF23 was substantially elevated in ADPKD patients compared with GFR-matched CKD patients, and was associated with an apparent renal phosphate leak, while PTH and vitamin D metabolite levels remained in the normal range. This suggests that the marked increase of FGF23 in early stage ADPKD represents a previously unrecognized manifestation of ADPKD.

Results

Patient characteristics

Table 1 shows the characteristics of 100 patients with ADPKD (mean age 31 years, 64% male), 20 patients with non diabetic chronic kidney disease (NDCKD) (mean age 37 years, 40% male), 26 patients with diabetes mellitus Type 2 (DM2) (mean age 57 years, 81% male) and 20 healthy volunteers (mean age 32 years, 60% male). The estimated GFR was similar in all groups (mean estimated GFR 94 ml/min/1.73 m^2 in ADPKD, 98 ml/min/1.73 m^2 in NDCKD, 92 ml/min/1.73 m^2 in patients DM2 and 99 ml/min/1.73 m^2 in healthy volunteers). The mean total kidney volume was 967±534 cm^3 in ADPKD patients. ADPKD related symptoms such as flank pain, past episodes of macrohematuria and cyst infection were reported in up to 30% of the patients. Chronic glomerulonephritis was present in 18 patients of the NDCKD patients (biopsy-proven in 14 patients) and 2 patients had ischemic nephropathy. In patients with DM2, the mean diabetes duration was 8±5 years, the mean glycosylated hemoglobin (HbA1c) level was 8.6±1.0% and the anti-diabetic treatment included insulin and oral drugs. The kidneys of the healthy volunteers were normal by ultrasound examination with a mean total kidney volume of 360±80 cm^3. The median urinary excretion of albumin and the prevalence of microalbuminuria were similar in ADPKD and

NDCKD patients. None of the patients or volunteers received treatment with vitamin D, vitamin D analogues, calcium supplementation, phosphate binders or bisphosphonates.

FGF23, serum phosphate and urinary phosphate reabsorption

The mean c-term FGF23 level in the ADPKD group amounted to 163 RU/ml and was significantly higher than in NDCKD patients (44 RU/ml), patients with DM2 (40 RU/ml) and healthy volunteers (28 RU/ml) (Table 2). The FGF23 levels were similar in NDCKD, DM2 and healthy volunteers groups. Ninety-nine percent of ADPKD patients, none of NDCKD patients, 15% of patients with DM2 and none of the healthy volunteers had a c-term FGF23 level above 100 RU/ml. The difference between ADPKD patients and the other two patient groups with CKD remained significant independent of the level of albuminuria, estimated GFR, measured creatinine clearance or the presence of hypertension. The higher c-term FGF23 levels in ADPKD patients were independent of renal function and age (Figure 1).

Intact FGF23 and c-term FGF23 levels were measured simultaneously in a subset of 10 serum samples of ADPKD patients. There was a highly significant correlation between c-term FGF23 levels measured by the Immutopics assay and intact FGF23 levels measured by the Kainos assay (r^2=0.68, P=0.003) without difference between the assay means (0±39 RU/ml, P=0.99).

Since FGF23 promotes phosphate excretion by the kidney we examined phosphate metabolism in detail. Table 2 shows that the mean serum phosphate levels were lowest in ADPKD patients (0.92 mmol/l in ADPKD patients, 1.04 mmol/l in NDCKD patients, 0.96 mmol/l in DM2 patients and 1.01 mmol/l in healthy volunteers. The mean difference (95% CI) of serum phosphate levels between ADPKD patients and NDCKD patients was -0.11 (-0.21 to -0.02) mmol/l. The serum phosphorus levels were similar in NDCKD, DM2 and healthy volunteers groups. Figure 2A depicts the relative frequency distribution per 0.1 mmol/l interval of serum phosphate for ADPKD patients, NDCKD patients and healthy

volunteers. The number of patients with hypophosphatemia as defined by serum phosphate level <0.87 mmol/l was highest in the ADPKD group (38%), compared with NDCKD patients (25%), DM2 patients (27%) and healthy volunteers (5%). Moreover the tubular maximum of phosphate reabsorption per glomerular filtration rate (TmP/GFR) was lowest in ADPKD patients (0.81 mmol/L GF in ADPKD patients, 0.92 mmol/L GF in NDCDK patients and 0.88 mmol/L GF in healthy volunteers). Figure 2B displays the relative frequency distribution per 0.1 mmol/L GF interval of TmP/GFR for ADPKD patients, NDCKD patients and healthy volunteers, and reveals a strong prevalence of low TmP/GFR values in ADPKD patients compared with NDCKD patients and healthy volunteers. There was a very highly correlation between serum phosphate levels and TmP/GFR in ADPKD patients (r^2=0.86, P<0.0001), NDCKD patients (r^2=0.96, P<0.0001) and healthy volunteers (r^2=0.84, P<0.0001) (Figure 2C), suggesting that hypophosphatemia in all conditions was caused by a renal leak of phosphate. None of the study participants presented with hyperphosphatemia. The mean 24h urinary phosphate excretion was similar in ADPKD, NDCKD patients and healthy volunteers (21 mmol in ADPKD patients, 25 mmol in NDCKD patients and 25 mmol in healthy volunteers) and the significant difference of FGF23 levels between ADPKD patients and NDCKD patients and healthy volunteers was independent of the daily urinary phosphate excretion (Table 2). These data show that the renal phosphate leak causes a high prevalence of hypophosphatemia in ADPKD patients.

Parathyroid hormone, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels

To elucidate whether the differences in serum phosphate and TmP/GFR were associated with differences in serum levels of other hormones known to influence phosphate homeostasis, serum intact PTH, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were measured in ADPKD patients, NDCKD patients and healthy volunteers. Mean intact PTH (49±16 ng/ml in ADPKD, 35±12 ng/ml in NDCKD and 43±16 ng/ml in healthy

volunteers), 25-hydroxyvitamin D (20±8 µg/l in ADPKD, 19±10 µg/l in NDCKD and 25±12 µg/l in healthy volunteers) and 1,25-dihydroxyvitamin D levels (50±15 ng/l in ADPKD, 53±27 ng/l in NDCKD and 51±10 ng/l in healthy volunteers) remained in the normal range in patients with CKD stage 1 and 2 and healthy volunteers (Figure 3). Thus, the elevation of FGF23 in patients with ADPKD and normal or subnormal GFR appears to be a derangement which is specific for ADPKD and does not appear to be related to changes in other key hormones that regulate phosphate.

Discussion

The present study shows that ADPKD patients with CKD stage 1 and 2 have 4-fold elevated levels of serum FGF23, whereas PTH, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D levels remained in the normal range. The rise in FGF23 was accompanied by a renal leak of phosphate, as evidenced by the strong prevalence of low TmP/GFR and by the tight and positive correlation between TmP/GFR and serum phosphate levels. Stated in another way, FGF23 appears to be functionally active, at least at the level of the renal phosphate transport.

Conceptually, FGF23 secretion in CKD is meant to be triggered by phosphate retention as a counteracting mechanism to restore neutral phosphate balance in the face of decreased renal function. In our study, mean estimated GFR and measured creatinine clearance were approximately 100 ml/min in ADPKD patients. Thus it appears unlikely that retention of phosphate due to impaired renal function triggered FGF23 secretion. Moreover in two separate cohorts of CKD stage 1 and 2 patients, FGF23 levels were comprised within the normal range. Therefore, the observation made herein appears as specific for ADPKD.

Previous studies have examined FGF23 levels in patients at early CKD stages. Firstly, it is noteworthy that the serum levels of FGF23 and of phosphate previously reported in patients with CKD 1 and 2[11-17] were similar to those obtained in our patient groups with

diabetic and non diabetic nephropathy. Fliser et al. studied FGF23 concentration as a marker for CKD progression and found that the levels of FGF23 steadily increased with decreasing levels of GFR.[12] In that study, CKD patients at stage 1 displayed c-terminal FGF23 levels of 57 RU/ml that increased to 81 RU/ml in CKD stage 2, values which are significantly lower than those measured in our ADPKD cohort. Mean serum phosphate levels were not decreased in CKD stage 1 (1.02 mmol/l) and 2 (1.0 mmol/L) and showed a tendency to increase in CKD stage 3 (1.08 mmol/l). In the study by Gutierrez et al. CKD stage 1 and 2 patients were reported to have a mean c-term FGF23 levels of 86 RU/ml, like in the study of Fliser et al., and serum phosphate values were also reported to be within the normal range with a tendency to rise with decreasing renal function.[11] Notably, both studies reported a parallel increase of intact PTH levels that was already apparent at CKD stage 2, whereas in our study, PTH levels were normal, further indicating an independent mechanism of enhanced FGF23 secretion in ADPKD patients. In both aforementioned studies by Fliser et al. and Gutierrez et al., 3% and 16% respectively of the study participants were ADPKD patients; however GFR and FGF23 levels were not reported for this subgroup of patients.

Our findings demonstrate that ADPKD patients display FGF23 levels that are inappropriately high for the degree of severity of renal insufficiency, that mediate a renal phosphate leak and consequently lead to low serum levels of phosphate. Our study suggests that the high levels of FGF23 observed in ADPKD patients are specific to that disease. What could be the explanation for this specificity? FGF23 is also expressed in the liver[18] and ADPKD involves the liver which could have altered the metabolism of FGF23. However, in our cohort of young ADPKD patients only 5% of them showed cystic liver disease and in most of them only few liver cysts were detected by MRI. Since in all ADPKD patients liver enzymes were in the normal range (data not shown) we considered unlikely that the aforementioned disorder of FGF23 metabolism could originate in the liver.

The Immutopics FGF23 assay detects c-terminal fragments along with its biologically active moiety. It may be speculated that these fragments accumulate in patients with ADPKD due to an altered metabolism, which could account for the elevated c-term FGF23 levels. Therefore, we measured intact FGF23 using the Kainos assay in a subset of ADPKD patients. The difference of the mean between these two assays was very small, indicating that FGF23 fragments did not accumulate in our ADPKD patients and that the elevated levels of c-term FGF23 reflect biologically active FGF23, what is further supported by the observed renal leak of phosphate. Actually, our results are in line with a previous study in which the relationship between different FGF23 assays were tested in normophosphatemic individuals.[19]

It is fair to state that the stimulus driving FGF23 secretion in patients with CKD is incompletely understood. It is tempting to postulate that the synthesis of FGF23 is induced by changes in intracellular phosphate in response, for instance to chronic loads in dietary phosphate. Along that line it could be speculated that for unknown reasons our ADPKD patients would chronically ingest more phosphate than the volunteers and CKD patients, and that this higher amount of phosphate would be triggering an increase of FGF23 secretion.[20] However, such was not the case because there was no difference in 24h urine excretion rate of phosphate between the 3 groups. In additional, Isakova et al. showed that an acute oral phosphate and calcium load did not change FGF23 levels in normophosphatemic and normocalcemic CKD patients[21] and it would be surprising that differences in phosphate intake among the four groups could explain a 4-fold increase of FGF23 levels in ADPKD patients.

Although renal cysts are the most prominent feature of the disease, ADPKD is a systemic disorder that involves heart and vessels, liver, pancreas and lung.[22-24] Interestingly, polycystin-1 is highly expressed in osteoblasts and osteocytes, the main sources for FGF23 production.[25] Targeted disruption of *Pkd1* in mice causes severe defects in bone development, suggesting that polycystin-1 plays a major role in the embryonic formation of cartilage and bone.[26-30] Conditional disruption of *Pkd1* in osteoblasts leads to bone loss in mice, suggesting

that polycystin-1 regulates bone metabolism although the mechanism still needs to be determined.[31] It could be hypothesized that polycystin-1 is directly implicated in the regulation of FGF23 production, and that a genetic defect of polycystin-1 as the one occurring in ADPKD is responsible for the increased FGF23 secretion. In contrast to the role of polycystin-1 in bone formation and metabolism in rodents, an ADPKD specific alteration of bone metabolism has so far not been reported in human ADPKD disease. Thus the clinical consequences of an enhanced FGF23 secretion in ADPKD patients are currently unknown.

In conclusion, the finding of elevated FGF23 levels in ADPKD with normal renal function, normal PTH and apparent renal leak of phosphate represents a previously unrecognized manifestation of ADPKD. However, further studies are needed to unmask the mechanism governing this disorder.

Methods

Study participants and procedures

ADPKD patients enrolled in this study belong to the well characterized prospective SUISSE ADPKD cohort.[32] Patients with previously known ADPKD or with a positive family history for the disease had been screened for enrolment and the diagnosis of ADPKD was based on ultrasonographic diagnostic criteria.[33] Patients aged 17-40 years with an estimated creatinine clearance ≥70 ml/min were enrolled. As a comparison to the ADPKD cohort, we studied patients with DM2, aged >18 years with a HbA1c level >7.5% and an estimated GFR ≥70 ml/min, patients with NDCKD, aged >18 years with an estimated GFR ≥70 ml/min and healthy volunteers, aged 17-40 years without history of renal disease, hypertension or diabetes.

Detailed medical history was obtained from all patients and healthy volunteers, including previous hospitalization and medication. Sitting blood pressure was measured by a nurse after a rest of 5 minutes. Subjects were declared as having arterial hypertension if systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) were found elevated (SBP ≥140 mm Hg, DBP ≥90 mm Hg) or treatment with an antihypertensive drug was recorded. On the morning of the study day and after an overnight fast, a blood sample was drawn. A 24h urine collection was obtained on the day prior to the visit to the clinic. A fasting spot urine sample was collected after voiding the first urine of the day prior to attending the clinics in ADPKD patients and volunteers. Serum and spot urine aliquots were stored at -80°C prior to analysis. Blood was analyzed for FGF23, PTH, phosphate, creatinine, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. Spot urine was analyzed for phosphate and creatinine. 24h urine was analyzed for creatinine and phosphate in the ADPKD, NDCKD and healthy volunteer group. All ADPKD patients underwent renal magnetic resonance imaging (MRI) without contrast media. Total kidney volumes were estimated from MRI sequences as reported previously.[2] The healthy volunteers underwent renal ultrasonography and the kidney volumes were estimated by applying the ellipsoid formula.[34]

All patients were studied at the University Hospital of Zürich, Switzerland between January 2004 and May 2010. The study was conducted according to the Declaration of Helsinki and the guidelines of Good Clinical Practice (GCP). Study approval was obtained from the local Ethics Committee, and all patients and healthy volunteers gave written, informed consent.

Analytical methods

The levels of carboxy-terminal FGF23 (c-term FGF23, 1st generation, Immutopics Inc., San Clemente CA, USA), intact FGF23 (intact FGF23, Kainos Laboratories Inc., Tokyo,

Japan) and intact PTH (Biomerica Inc., Newport Beach CA, USA) were measured by ELISA according to the manufacturer's protocol. Serum 25-hydroxyvitamin D has been determined using the RIA-kit from Diasorin (Stillwater, MN, USA), serum 1,25-dihydroxy vitamin D was measured by radioimmunoassay (immunodiagnostic systems, Fountain Hills, AZ, USA). Phosphate concentrations were measured in serum and urine using standard methods. Creatinine was assayed by the IDMS traceable modified Jaffé method. Albumin was measured on a Integra system (Roche, Rotkreuz, Switzerland), using immunoturbidimetry. Inter-assay and intra-assay coefficient of variation were below 5% for the determination of albumin, creatinine and phosphate, below 10% for the quantification of 25-hydroxyvitamin D and below 13% for 1,25-dihydroxyvitamin D. TmP/GFR in mmol/L of glomerular filtrate (GF) was calculated according to the formula of Brodehl.[35] The glomerular filtration rate was estimated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[36]. Hypophosphatemia and hyperphosphatemia were defined as serum phosphate levels <0.87 mmol/l and >1.45 mmol/l, respectively.

Statistical Analysis

Differences among the four groups were compared by one-way analysis of variance. When the difference was significant, statistical comparison of the ADPKD with the NDCKD patients, DM2 patients and healthy volunteers were performed, using Dunnett's post hoc test with the NDCKD as reference group. Differences among these groups in categorical data were compared by the Chi square test. Univariate Pearson's correlation was used to test for associations between continuous variables. All P values were two-sided for the comparison between the groups and values below 0.05 were considered as statistically significant. Statistical analyses were performed using SAS statistical software version 9.2. (SAS Institute Inc., Cary, NC).

Disclosure

All authors declared no competing interests.

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Table 1
Characteristics of patients with autosomal dominant polycystic kidney disease (ADPKD), with diabetes mellitus type 2 (DM 2), with non diabetic chronic kidney disease (NDCKD) and of healthy volunteers (HV). *

Characteristic	**ADPKD**	**NDCKD**	**DM2**	**HV**
	N = 100	**N = 20**	**N = 26**	**N = 20**
Age – years	31 (6)	37 (17)	57 (10)	32 (5)
Sex – no. (%)				
Female	36 (36)	12 (60)	5 (19)	8 (40)
Male	64 (64)	8 (40)	21 (81)	12 (60)
BMI – kg per m^2	24 (4)	24 (3)	30 (3)	24 (2)
Estimated glomerular filtration rate† – milliliter per minute per 1.73 m^2	94 (18)	98 (18)	92 (14)	99 (12)
Chronic kidney disease classification – no. (%)‡				
Stage 1	53 (53)	13 (65)	14 (54)	
Stage 2	46 (46)	7 (35)	12 (46)	
Stage 3	1 (1)	0 (0)	0 (0)	
Urinary albumin excretion – milligram per day	47 (27 – 97)	44 (14 – 264)	10 (5 – 17)	6 (4 – 9)
Blood pressure – mm Hg				
Systolic	131 (16)	131 (8)	131 (11)	123 (7)
Diastolic	83 (11)	84 (5)	85 (10)	74 (6)
Antihypertensive treatment – no. (%)				
ACEi/ARB	37 (37)	16 (80)	18 (69)	0 (0)
Thiazide diuretic	9 (9)	1 (5)	10 (38)	0 (0)
Others	7 (7)	0 (0)	5 (19)	0 (0)

* Table shows the mean (standard deviation), the median (interquartile range) or number of patients (percent).

† The glomerular filtration rate was estimated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[36]

‡ Chronic kidney disease was classified according to the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation.[37] Stage 1 denotes glomerular filtration rate (GFR, milliliter per minute per 1.73 m^2) more than 90, stage 2 to 60 to 89 and stage 3 to 30 to 59.

BMI denotes body mass index and ACEi/ARB angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker.

Table 2
Parameters of phosphate metabolism in patients with autosomal dominant polycystic kidney disease (ADPKD), non diabetic chronic kidney disease (NDCKD), diabetes mellitus type 2 (DM2) and in healthy volunteers (HV).

Parameter	ADPKD N=100	NDCKD N=20	DM2 N = 26	HV N=20	P
Fibroblast growth factor 23 – relative unit per milliliter	163 (33)	44 (18)	40 (56)	28 (22)	<0.0001
Mean difference from CKD	120†	Reference	-3	-16	
95% CI	99 to 140		-28 to 21	-43 to 10	
Serum phosphate – millimol per liter	0.92 (0.17)	1.04 (0.22)	0.96 (0.17)	1.01 (0.12)	0.007
Mean difference from CKD	-0.11†	Reference	-0.08	-0.02	
95% CI	-0.21 to -0.02		-0.18 to 0.04	-0.15 to 0.10	
TmP/GFR – millimol per liter per glomerular filtration	0.81 (0.18)	0.92	NA	0.89 (0.12)	0.04
Mean difference from CKD	-0.10†	Reference		-0.04	
95% CI	-0.21 to -0.01			-0.16 to 0.09	
24h renal phosphate excretion – millimol per 24 hours	21 (13)	25 (10)	NA	25 (11)	0.2
Mean difference from CKD	-4	Reference		1	
95% CI	-11 to 3			-9 to 10	
Measured creatinine clearance – milliliter per minute per 1.73 m^2	99 (25)	111(18)	NA	113 (49)	0.1
Mean difference from CKD	-11	Reference		2	
95% CI	-29 to 6			-20 to 24	

* Table shows the mean (standard deviation).

† Significant for an alpha level of 0.05, post hoc Dunnett's test with NDCKD values as reference.

CI denotes confidence interval, TmP/GFR tubular maximum phosphate reabsorption per glomerular filtration rate, and GF glomerular filtration.

Figure legends

Figure 1.

A) Scatter plot of carboxy-terminal fibroblast growth factor 23 (c-term FGF23) levels versus estimated glomerular filtration rate (eGFR) and B) versus age of 100 patients with autosomal dominant polycystic kidney disease (ADPKD), 20 patients with non diabetic chronic kidney disease (NDCKD), 26 patients with diabetes mellitus type 2 (DM2) and 20 healthy volunteers (HV). Symbols represent individual patients, bold circles indicate ADPKD patients, open squares NDCKD patients, open triangles DM2, and open circles HV.

Figure 2.

Relative frequency distribution A) per 0.1 mmol/l interval of serum phosphate (PO4) and B) per 0.1 mmol/ml for tubular maximum phosphate reabsorption per glomerular filtration rate (TmP/GFR) in 100 patients with autosomal dominant polycystic kidney disease (ADPKD), 20 non diabetic chronic kidney disease patients (NDCKD) and 20 healthy volunteers (HV). C) Correlation between TmP/GFR and serum PO4 in 100 ADPKD patients (r^2=0.86, 95% CI 0.90 to 1.06, P<0.0001), 20 NDCKD patients (r^2=0.96, 95% CI 0.85 to 1.08, P<0.0001) and in 20 HV (r^2=0.84, 95% CI 0.76 to 1.18, P<0.0001). Symbols represent individual patients, bold circles indicate ADPKD patients, open squares NDCKD patients, and open circles HV. Respective lines of linear regression are shown for each group.

Figure 3.

A) Carboxy-terminal fibroblast growth factor 23 (c-term FGF23) B) intact parathyroid hormone (iPTH), C) 25-hydroxyvitamin D (25(OH) D) and D) 1,25-dihydroxyvitamin D ($1,25(OH)_2$ D) levels stratified for estimated glomerular filtration rate (eGFR) between 60-<90, and > 90 ml/min per 1.73m^2 in patients with autosomal dominant polycystic kidney disease (ADPKD), non diabetic chronic kidney disease (NDCKD) patients and healthy volunteers (HV).

Figure 1

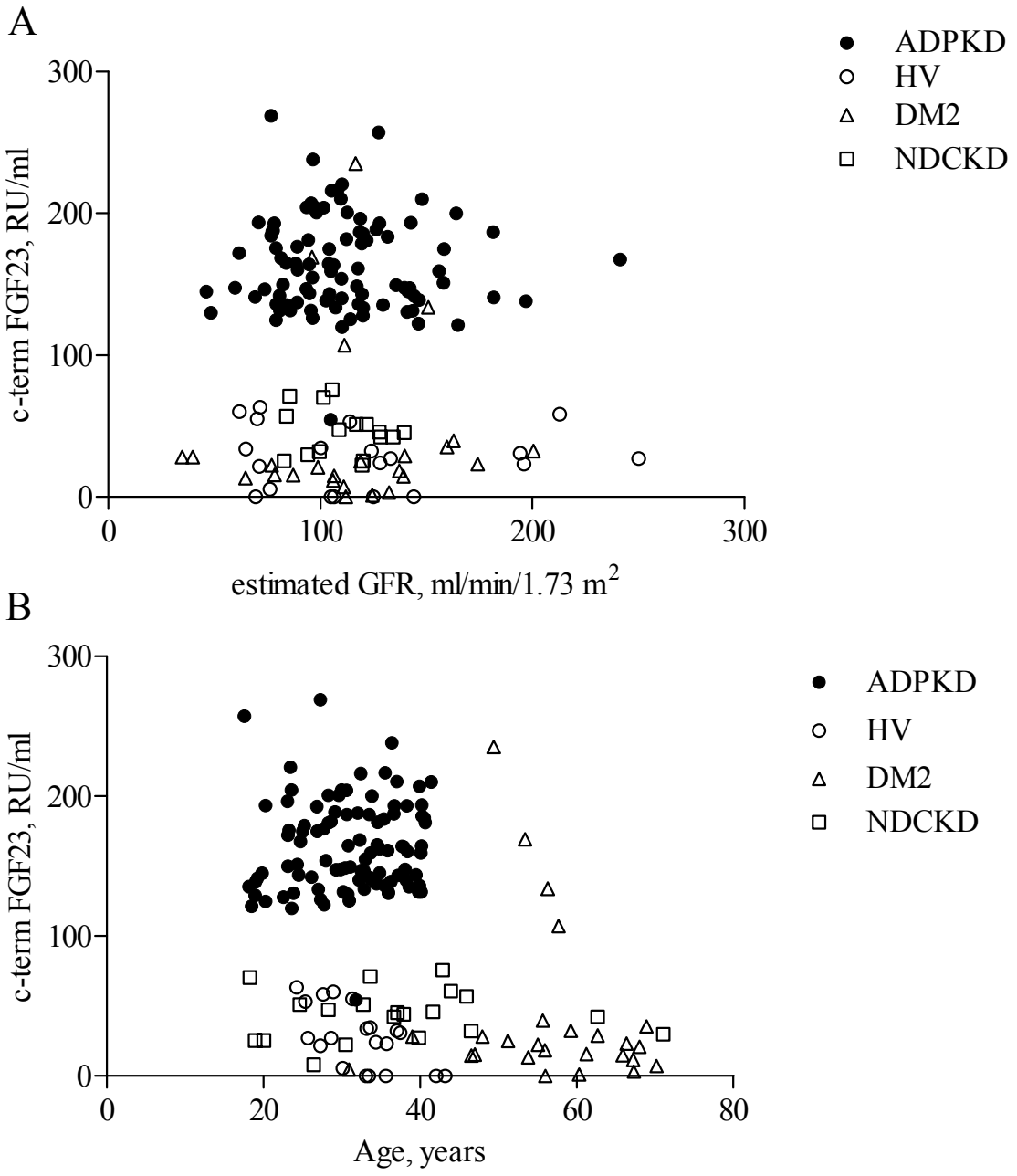

A
ADPKD
HV
DM2
NDCKD
c-term FGF23, RU/ml
300
200
100
0
0
100
200
300
estimated GFR, ml/min/1.73 m2
B
ADPKD
HV
DM2
NDCKD
c-term FGF23, RU/ml
300
200
100
0
0
20
40
60
80
Age, years

Figure 2

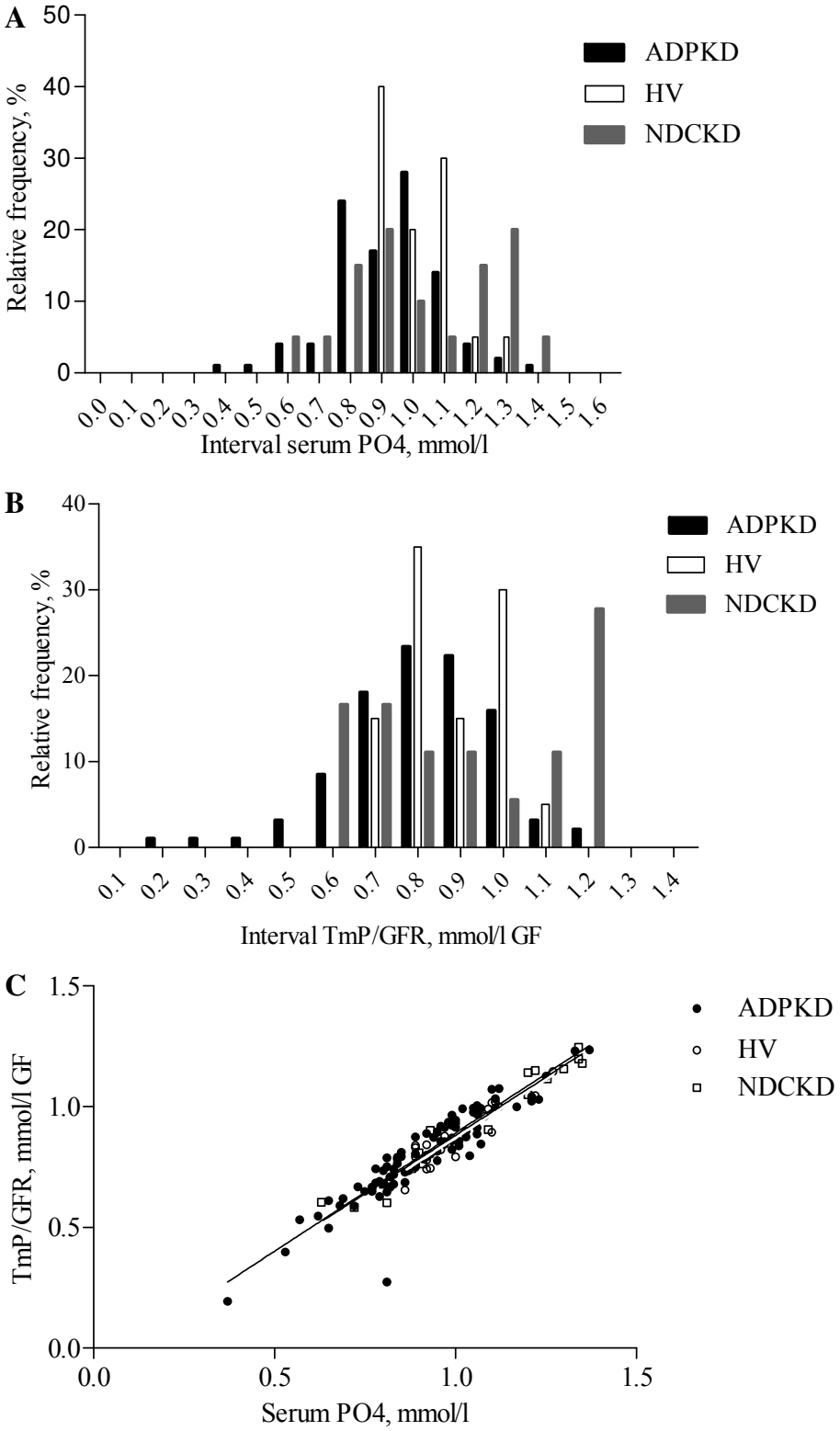
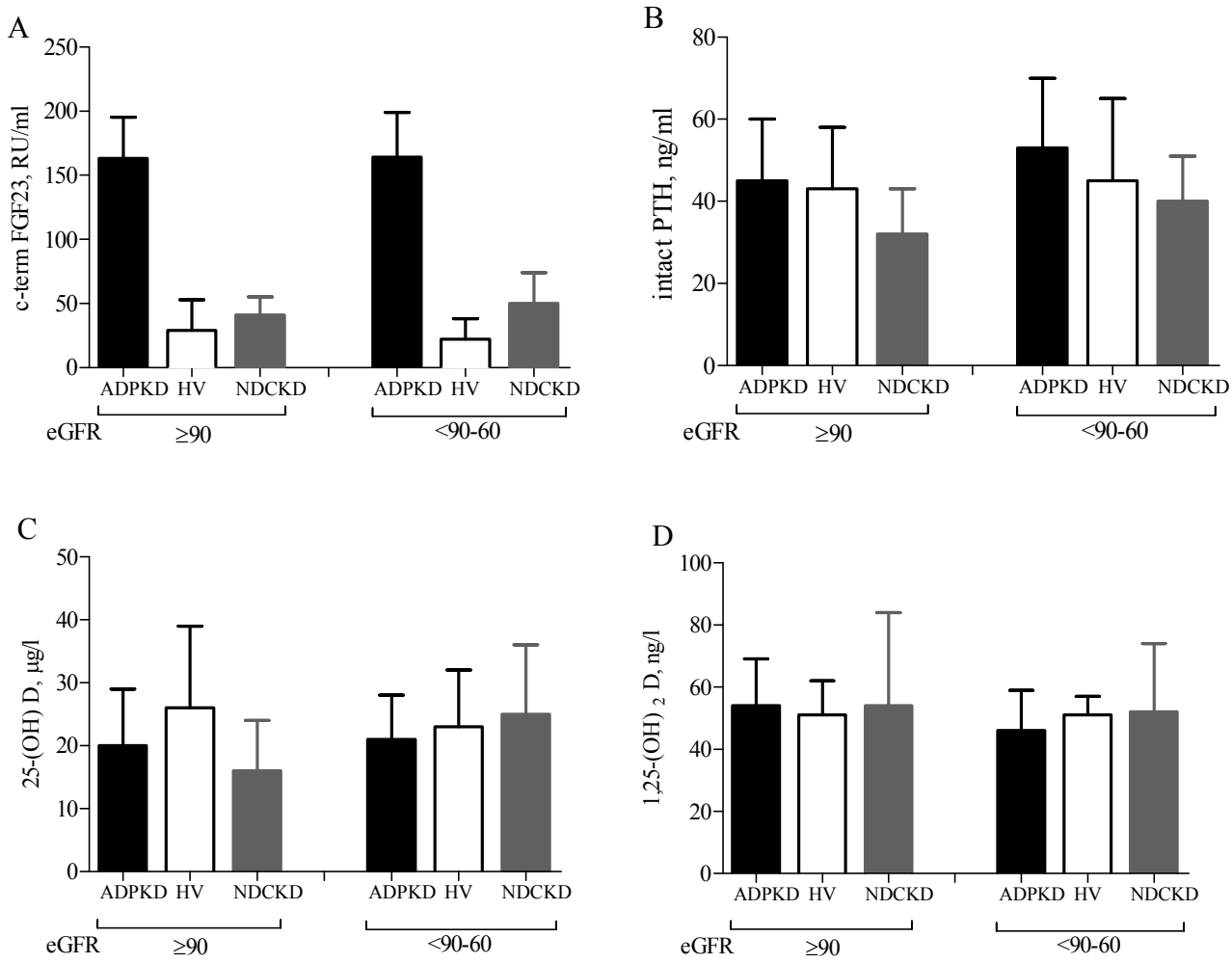

A
Relative frequency, %
Interval serum PO4, mmol/l
ADPKD
HV
NDCKD
B
Relative frequency, %
Interval TmP/GFR, mmol/l GF
ADPKD
HV
NDCKD
C
TmP/GFR, mmol/l GF
Serum PO4, mmol/l
ADPKD
HV
NDCKD

Figure 3


A
c-term FGF23, RU/ml
250
200
150
100
50
0
ADPKD HV NDCKD
ADPKD HV NDCKD
eGFR ≥90
<90-60
B
intact PTH, ng/ml
80
60
40
20
0
ADPKD HV NDCKD
ADPKD HV NDCKD
eGFR ≥90
<90-60
C
25-(OH) D, µg/l
50
40
30
20
10
0
ADPKD HV NDCKD
ADPKD HV NDCKD
eGFR ≥90
<90-60
D
1,25-(OH)2 D, ng/l
100
80
60
40
20
0
ADPKD HV NDCKD
ADPKD HV NDCKD
eGFR ≥90
<90-60